COMPARISON OF EFFICACY AND SAFETY SILODOSIN 8 MG ONCE DAILY AND SILODOSIN 4 MG TWICE DAILY IN BPH PATIENTS WITH LUTS.

[1]Ramzie Nendra Diansyah, [1]Johan Renaldo, [1]Wahjoe Djatisoesanto, [1]Lukman Hakim.

[1]Department of Urology, Faculty of Medicine/Universitas Airlangga, Soetomo General Hospital, Surabaya.

ABSTRACT

Objective: *This study was aimed to compare the efficacy and side effect of silodosin 8mg once daily and silodosin 4mg twice daily in BPH-LUTS patients after 4 and 12 weeks.* ***Material & Methods:*** *Single blind randomized controlled trials in 60 male patients aged ≥ 45 years with BPH-LUTS from July 2017 to October 2017 was divided into groups who received 8mg of silodosin once daily and those who received 4mg of silodosin twice daily. Efficacy and adverse events were evaluated after 4 and 12 weeks of treatment.* ***Results:*** *There was no significant difference of mean age of the two groups was 67.93 ± 6.49 years and 69.07 ± 6.28 years respectively (p 0.49). Both doses of this drug decreased the International Prostate Symptom Score (IPSS) and significantly increased the maximum urinary flow (Qmax) (p<0.05) but there was no significant differences between the two groups (p>0.05). Ejaculation disorder was the most common side effect in all groups (6.7% and 5%) and there was no significant difference between the two groups(p>0.05).* ***Conclusion:*** *The administration of 8mg of once daily silodosin has similar efficacy as 4mg twice daily silodosin. There were no adverse events differences in the two groups. Ejaculation disorder is the most common adverse event of silodosin administration.*

Keywords: *Benign Prostatic Hyperplasia, Lower Urinary Tract Symptoms, International Prostate Symptom Score, Qmax, Ejaculation Disorder.*

ABSTRAK

Tujuan: *Penelitian ini bertujuan untuk membandingkan efikasi dan efek samping pemberian silodosin 8mg satu kali sehari dan silodosin 4mg dua kali sehari pada pasien Benign Prostatic Hyperplasia (BPH) dengan Lower Urinary Tract Symptoms (LUTS) pada minggu ke 4 dan 12.* ***Bahan & Cara:*** *Penelitian single blind randomized controlled trial pada 60 pasien pria ≥45 tahun dengan BPH-LUTS dari Juli sampai Oktober 2017 yang terbagi dalam kelompok yang mendapatkan silodosin 8mg satu kali sehari dan kelompok yang mendapatkan silodosin 4mg dua kali sehari. Efikasi dan efek samping di evaluasi setelah pemberian 4 dan 12 minggu pengobatan.* ***Hasil:*** *Rerata usia kedua kelompok tidak didapatkan perbedaan yang signifikan masing-masing 67.93 ± 6.49 tahun dan 69.07 ± 6.28 tahun (p 0.49). Kedua dosis obat ini sama-sama menurunkan International Prostate Symptom Score (IPSS) dan meningkatkan nilai laju pancaran maksimal urine (Qmax) secara signifikan (p<0.05) tetapi tidak ada perbedaan signifikan antara kedua kelompok (p>0.05). Gangguan ejakulasi merupakan efek samping terbanyak pada semua kelompok (6.7% dan 5%) dan tidak terdapat perbedaan yang bermakna dari keduanya (p>0.05).* ***Simpulan:*** *Pemberian silodosin 8mg satu kali sehari mempunyai efikasi yang sama dengan silodosin 4mg dua kali sehari. Tidak ada perbedaan efek samping dari kedua kelompok tersebut. Gangguan ejakulasi adalah efek samping yang paling banyak ditemukan dari pemberian silodosin.*

Kata Kunci: *Benign Prostatic Hyperplasia, Lower Urinary Tract Symptoms, International Prostate Symptom Score, Qmax, gangguan ejakulasi.*

Correspondence: Lukman Hakim, c/o: Department of Urology, Faculty of Medicine/Universitas Airlangga, Soetomo General Hospital, Surabaya. Jl. Mayjend. Prof. Dr. Moestopo 6-8, Surabaya 60286. Phone: +62 31 5501318; Fax: +62 31 5024971. Email: lukman0908@gmail.com.

INTRODUCTION

Benign Prostatic Hyperplasia (BPH) is a benign prostatic enlargement condition that can be accompanied by Lower Urinary Tract Symptoms (LUTS). BPH arises in the prostate gland in periuretral and transitional zones in elderly male populations. BPH rarely occurs before the age of 40 years. About 50% of men get symptoms associated with BPH at 50 years of age. Incidence of BPH

increased 10% per decade and reached approximately 80% at 80 years old. Enlargement of prostate gland resulting in disruption of the flow of urine, causing interference of micturition.[1,2] Clinically BPH is associated with the syndrome of the lower urinary tract commonly referred to as Lower Urinary Tract Symptoms (LUTS) resulting of the enlargement of the prostate gland.[3] As many as 50% of the population of men aged over 50 years found to have LUTS associated with BPH. Approximately 13% of men over 40-49 years old have moderate and severe International Prostate Symptom Score (IPSS), whereas at age >70 years it increases to 28%.[4] The possibility of maximum urinary flow (Qmax) <15ml/s increased in men over 50 years. Age is the most significant risk factor for BPH incidence and LUTS occurrence.[5]

Food and Drug Administration (FDA) has endorsed the new selective α1A adrenergic receptor antagonist called silodosin. Silodosin previously known as KMD-2312 is absorbed rapidly with bioavailibility of 32% when given a dose of 8 mg per day. Silodosin reached the maximum concentration in plasma in a rapid time of 2.6 ± 0.90 hours with a concentration of 61.6 ± 27.54 ng/mL. The half-life of the silodosin is 13-14 hours. The silodosin metabolite is K3213G has an AUC (area under curve) four times fold greater than tamsulosin. Silodosin is metabolized by the liver and eliminated through the feces (54.9%) and urine (33.5%).[6]

Silodosin at a dose of 4 mg twice daily has been approved by countries in Asia and is widely used. However, once a dose of 8 mg once daily has been developed to improve the comfort of consuming and provide optimal effects for 24 hours. Research on healthy men shows that 8 mg once daily a silodosin has good pharmacokinetics and safety.[7]

OBJECTIVE

This study was aimed to compare the efficacy and side effect of silodosin 8mg once daily and silodosin 4mg twice daily in BPH-LUTS patients after 4 and 12 weeks.

MATERIAL & METHODS

In this study we performed single blind randomized controlled trials in 64 male patients with LUTS associated with BPH. We evaluated the efficacy and side effect after 4 and 12 weeks administration of oral silodosin. The inclusion criteria were male patients with bothersome LUTS caused by BPH (prostate volume ≥ 20 ml) with IPSS ≥ 8 and Qmax < 15 mL/s who were just diagnosed or previously had alpha blockers medication, with age ≥ 45 years old and consent and willing to join the study. Exclusion criteria from this study included urinary retention, urethral stricture, BPH-LUTS with complications such elevation of creatinine serum more than 1.4 mg/dl, sepsis, stone in lower urinary tract and hernia inguinalis. The other conditions were excluded: had a previous any prostate surgery or pelvic radiation, severe orthostatic hypotension, uncontrolled diabetes melitus, post stroke and to be suffering from prostate malignancy from ten core biopsy. All the patients were randomized being two groups. 32 patients receive 8 mg silodosin once daily that given 2 silodosin 4 mg after breakfast and 1 placebo after dinner (group I). The other group, 32 patients was given silodosin 4 mg twice daily, 4 mg silodosin and 1 placebo after breakfast then 4 mg silodosin after dinner (group II).

We measured the efficacy of two doses administration of silodosin based on the IPSS score and Qmax value from baseline and after 4 weeks and 12 weeks therapy. At the same time the safety profiles were evaluated from the measurement of blood presure, to know the orthostatic hypotension condition and ejaculations disorder by assessing IIEF-OF score associated therapy.

RESULTS

This study was conducted during July 2017 to October 2017, to evaluate the efficacy and adverse events of silodosin therapy 8 mg once daily and silodosin 4 mg twice daily in patients with BPH with LUTS, with the number of samples entering inclusion criteria of 64 patients with each group had 32 patients. There were 4 patients dropped out, 2 patients from group I and 2 patients from group II before the first evaluation (4 weeks) because of the adverse effects of ejaculatory disorders. 23 patients had taken different drugs to reduce LUTS complaints and had to undergo a wash-out period for 2 weeks before treatment.

Statistically, age, initial IPSS score as well as the initial Qmax of the patients between the two groups did not get a significant difference. All patients aged over 50 years with mean age group silodosin 1 x 8 mg and 2 x 4 mg silodosin group respectively 67.93 ± 6.49 years and 69.07 ± 6.28 years (p 0.49). Most patients from both groups

suffered from moderate LUTS with mean IPSS of group I was 16.7 ± 4.65 and group II was 16 ± 5.29 (p 0.59). Likewise with the maximum urinary flow (Qmax) for each group, the average calculation of Qmax is 13.01 ± 1.06 ml/s in the group I and 12.97 ± 1.13 ml in the group II (p 0.87). A total of 11 patients from the Silodosin group I and 12 patients from group II, had previously received the tamsulosin for the previous LUTS. These patients had to undergo a wash-out period for 2 weeks with placebo to ensure prior drug elimination.

Based on the evaluation using the IPSS score, this study showed that the use of 8 mg once daily and 4 mg twice daily silodosin two times, statistically proved to decrease the IPSS score at week 4 and week 12 significantly. Furthermore, statistical analysis was performed to see which one was more superior, between silodosin 8 mg once daily and silodosin 4 mg twice daily for efficacy using unpaired T-test. In this study,we found in both groups had statistically equivalent IPSS score with initial IPSS score for group I was 16.70 ± 4.65, and group II was 16.00 ± 5.29, with p>0.05 (Table 2). After 4 weeks both groups showed a significant decrease in IPSS score, but statistically between the two groups there were no significant difference with p>0.05 (Table 2). Similarly at week 12, although both groups showed a significant decrease in IPSS score, but statistically between both groups there were no significant difference with p> 0.05 (Table 2). This suggests that administration of 8 mg once daily silodosin has equivalent efficacy to 4 mg twice daily silodosin to IPSS score.

This study also evaluated the efficacy between 8 mg once daily silodosin and 4 mg twice daily silodosin based on Qmax. Both dosage administrations statistically significant proved to be able to increase Qmax at 4th and 12th weeks evaluation. Furthermore, as in IPSS parameters, we evaluate the superior between both groups. We found both groups in this study had statistically equivalent Qmax value, with the initial Qmax value for group I was 12.97 ± 1.09 and group II was 12.97 ± 1.13 with p> 0,05. After 4 weeks, both groups showed a significant increase of Qmax, but statistically between the two groups there were no significant difference with p> 0.05 (Table 3). Similarly at week 12, although both groups showed a significant increase in Qmax, but statistically between both groups there were no significant difference with p> 0.05 (Table 3). This result showed that the efficacy of silodosin 8 mg once daily had equivalent efficacy to 4 mg twice daily silodosin to Qmax value.

This study also assessed the adverse events caused by each dose that given and it was compared. The safety evaluation were performed after 4 weeks of administration in 60 patients, had some adverse events of treatment were ejaculation disorder 9 patients (15%), 1 patient respectively suffering from orthostatic hypotension, nasal congestion, dry mouth, diarrhea or (1.7%) respectively.

In this study, we evaluated and assessed the adverse events after 12 weeks, with the result there were no difference after 4 and 12 weeks of treatment. The most common side effects were ejaculation disorders during of drug administration. The IIFF-OF (Orgasmic Function) questionnaire was used as a tool to assess the ejaculation disorders pre and post administration. IIEF Q9 (Question 9) and IIFF Q10

Tabel 1. Sample characteristics.

Variable	Group I	Group II	*P* value
N	32	32	
Age			
Mean (SD)	67.93 (6.49)	69.07 (6.28)	0.49*
Min - Max	54 - 83	57 – 88	
IPSS baseline			
Mean (SD)	16.70 (4.65)	16.00 (5.29)	0.59*
Min - Max	8 – 28	8 – 28	
*Qmax*baseline			
Mean (SD)	12.97 (1.09)	12.97 (1.13)	0.87*
Min - Max	10.80 – 14.90	10.00 – 14.70	

Group I:8 mg once daily; Group II: 4 mg twice daily; IPSS: International Prostate Symptom Score;
Qmax: maximum urinary flow; SD: standard deviation.
* Unpaired T test.

Table 2. Comparison of IPSS score after 4 and 12 weeks.

IPSS	Group I	Group II	*P* value
IPSS baseline			
Mean (SD)	16.70 (4.65)	16.00 (5.29)	0.59*
Min – Max	8 – 28	8 – 28	
IPSS 4th week			
Mean (SD)	13.23 (3.99)	12.27 (4.25)	0.36*
Min – Max	6 – 22	7 – 22	
IPSS 12th week			
Mean (SD)	9.23 (3.47)	9.07 (3.79)	0,86*
Min - Max	3 – 17	4 – 18	

* Unpaired T-test

Table 3. Comparison of Qmax after 4 and 12 weeks.

Qmax	Group I	Group II	*P* value
Qmax baseline			
Mean (SD)	12.97 (1.09)	12.97 (1.13)	0.98*
Min - Max	10.80 – 14.90	10.00 – 14.70	
Qmax 4th week			
Mean (SD)	13.86 (0.84)	14.23 (1.01)	0.13*
Min – Max	12.00 – 15.20	11.70 – 15.80	
Qmax 12th week			
Mean (SD)	15.82 (1.20)	15.70 (1.23)	0.69*
Min - Max	13.80 – 18.10	12.90 – 18.30	

* Unpaired T-test.

Table 4. Comparison of IIEF-OF score after 4 and 12 weeks

IIEF-OF	Group I	Group II	*P* value
IIEF-OF baseline			
Median (Min -Max)	9 (9-10)	9 (9-10)	0,87
IIEF-OF 4th week			
Median (Min -Max)	4 (4-5)	5 (4-5)	0,32
IIEF-OF 4th week			
Median (Min -Max)	4 (4-5)	5 (4-5)	0,32

*Mann -Whitney Test

(Question 10) represent ejaculatory complaints felt by the patient.

In subsequent studies conducted evaluation to see the greater adverse events between group I and group II. Based on statistical analysis using Mann-Whitney test, it can be seen that IIEF-OF score between both groups had approximately the same score ($p > 0.05$). Than the evaluation of both groups showed a statistically significant decrease in IIEF-OF score at week 4 and the score persisted until week 12, thus there were no statistically significant difference score between IIEF-OF week 4 and 12. This suggests that adverse events of silodosin 8 mg once daily group and 4 mg twice daily group are equivalent.

DISCUSSION

Benign Prostatic Hyperplasia (BPH) is a second common disease at urology outward clinic after urolithiasis in Indonesia. Similarly prevalence in any other countries, almost 70% men over 60

years old in United States have this disease, and strongly increase the risk become 90% in men over 80 years old. Accurate number incidence of BPH with LUTS in Indonesian's people not yet establish. BPH therapy have much variation, but all of that variation have one purpose that is improving patient's quality of life. Offered therapy to the patient based on symptoms, general condition, and individual objective caused by the disease. The choice start from watchful waiting, medical therapy and intervention. [8]

Silodosin is one of several drugs choice for medical therapy of BPH. This agent is α-1 long acting adrenoreceptor antagonist which is used to reduce prostate smooth muscle resistances as a dynamic component. Silodosin is reported to be 583 times more selective for α1A than for α1B, and 56 times more selective for α1A than for α1D receptors.[9]

Efficacy assessment by IPSS score, both dosage decrease IPSS score significantly from early score to 4 weeks evaluation and 12 weeks evaluation with $p< 0.05$ in every evaluation. Although in both group showed significantly decreasing of IPSS score but statistic analysis between both group did not different as well ($p> 0.05$). Based on IPSS score, we conclude that Silodosin 8 mg once daily have efficacy as well as Silodosin 4 mg twice daily.

Study from Marks et al, assess efficacy and side effect Silodosin 8 mg on BPH-LUTS through phase 3 randomised controlled study in US. Average age was 65 years old, 466 men given Silodosin 8 mg once daily, and 457 men given placebo for 12 weeks. Significant improvement of total IPSS already achieve in 3-4 days in Silodosin group (improvement -1.9 ; $p< 0.0001$). Improvement of storage IPSS -0.5 (p 0.0002) and voiding -1.4 ($p< 0.0001$) rather than placebo group. After 12 weeks, average total alteration baseline IPSS -4.2 than -2.3 between Silodosin and placebo ($p<0.0001$). There were no significantly different between Silodosin and placebo which can caused by the response of placebo, more than expectation with Tamsulosin did not significantly differ than placebo.[10]

Beside IPSS, another efficacy assessment with maximum urinary flow (Qmax) which compared before got the dosage and evaluation after 4 and 12 weeks with voided volume above 150 ml. Both groups showed a significant increase in Qmax, but statistically between both groups there were no significant difference with $p>0.05$. Similiarly with Marks et al, that average baseline changed Qmax more greater after Silodosin given (2.8-4.3) than placebo (1.5-2.8) (p 0.00021). This study showed that efficacy of Silodosin at evaluation for 4 weeks. Previous study tells that the onset of Silodosin was so quick, it can be evaluated by improvement of Qmax in 2-6 hours after first dosage given, parallel with decreased of irritation and obstructive IPSS subscore just in 3-4 days.[10] So, we can conclude that by efficacy silodosin 8 mg once daily not inferior than silodosin 4 mg twice daily.

There were almost none differ in efficacy nor than side effect. The purpose of improvement quality of life and Qmax was achieved. Choo et al, from Korean also showed that efficacy of Silodosin 8 mg once daily after breakfast not inferior than silodosin 4mg twice daily.[11] Sato et al, from Japan also publish similar result that overall silodosin 8 mg once daily was more comfortable and increase obedience to consumed if compared with silodosin 4 mg twice daily.[12]

Silodosin had an absolute bioavailability of 32%, and demonstrated linear pharmacokinetics over the dosage range of 0.1–48 mg/day. In healthy men whoreceived silodosin 8 mg once daily for 7 days, a mean maximum steady-state plasma concentration (Cmax) of 61.6 ng/mL was reached (tmax) in a mean 2.6 h. At steady state, the mean area under the plasma concentration timecurve (AUC) was 373.4 ng.h/mL. Steady statewas reached after administration of silodosin for 3 days.[13,14] The use of silososin 4 mg twice daily for 7 days on 5 voluntary healthy people, plasma concentration of this silodosin will reach a steady state on the third day. The accumulated factor relative to the first dose is 1.1 times.[15]

This study also assessed the efficacy and evaluated the side effect of both dosage, and compared which one who had more side effect than the other. Evaluation at 4 weeks after initial dose, side effect such as ejaculate disorder occurred in 9 patients (15%) who divided into 5 patients (8.3%) in group I and 4 patients (6.7%) in group II. However none patients were discontinued from medication even they experience this side effect until 12 weeks later. It can cause by as substantially older men in Indonesia were no longer sexual active and sexual satisfied not consideration anymore.

Others minimal adverse event in group I only one patient (1.7%) respectively were orthostatic hypotension, nasal congestion, dry mouth and diarrhea. While in group II, there were no side effect such as orthostatic hypotension, nasal congestion, dry mouth and diarrhea (0%). After 12 weeks

medication almost none alteration of adverse events, only in group I side effects of diarrhea that appeared at 4 weeks evaluation, became disappear at evaluation of 12 weeks. Furthermore, we need another clinical judgement and more evaluation to prove that diarrhea is possibly caused from silodosin adverse events or any other cause.

From 60 patients that administered silodosin 8 mg once daily, only one patient who suffers cardiovascular disorder that is orthostatic hypotension, but this patient still continued the research. It showed that type of adverse event remain mild and still tolerable. Morganroth et al, investigated Silodosin effect in 139 healthy men and showed that Silodosin 8 mg or 24 mg once daily did not effect heart rate, QT interval, PR interval or QRS complex, as a conclusion that no effect on ECG.[16]

Previous study from Marks dan Chapple et al, also publish the same result, silodosin make improvement LUTS after 3 weeks medication with orthostatic hypotension incidence was lower and did not effect the heart rate. Another compliance incidence besides orthostatic hypotension, such as headache and dizziness, were the same in patient with silodosin and patient with placebo. The orthostatic hypotension was characterized by decreasing systolic blood pressure more than 20 mmHg and diastolic blood pressure more than 10 mmHg in three minutes after laying down.[11,17] Silodosin showed safety long term profile like the study was continued in 9 months. Silodosin 8 mg did not have any serious side effect. Study of 435 total patients, side effects occurs such as ejaculate disorders (20.9%), diarrhea (4.1%), nasopharingitis (3.6%), orthostatic hypotension (2.6%) and dizziness (2.9%). Silodosin is well tolerated until 9 months evaluation with small incidence of headache and dizziness.[11]

Dizziness presentation was 3,2-5.1% in silodosin group compared to 1.2-4.5% in placebo, headache 0,9% in Silodosin group and 2,4% in placebo group. Orthostatic hypotension reported 1.5% in silodosin group and 2.6% in placebo.[18] Silodosin did not have any effect on heart rythm and none orthostatic hipotension episode post stimulation. Regard to European Medicines Agency's Commitee Products for Human Use, silodosin concomitant with antihypertensive agent doesn't increased risk the orthostatic hypotension.[19]

Common adverse event of silodosin was ejaculation disorder during alpha blocker administration. This disorder consist of orgasm without ejaculation, orgasm with reduced ejacu-lation and forced ejaculation. IEFF-OF questionnaire domain of ejaculation disorder especially used as tools for evaluate ejaculation disorder before and after silodosin medication. IEFF Q9 (Question 9) and IEFF Q10 (Question 10) represent patient ejaculation complaint based on Medical Dictionary of Regulatory Activities (MedDRA).[19]

Statistical analysis have significantly different from IIEF-OF score, from evaluation at 4 weeks and 12 weeks after silodosin 8 mg once daily administration ($p< 0.05$). However at 4 weeks and 12 weeks did not have changed the IIEF-OF Score. Similar result was seen in 4 mg twice daily group. This statistic result showed that there were no significant difference between both groups, so we concluded that side effect between two groups were equal.

Study from Caprogrosso et al, reported decreasing IIEF-OF Score based on Question 9 and 10 significantly in 64% patient with silodosin especially in younger age.[20] Nagai et al, found silodosin effect in three healthy patients, the evaluation of seminal flow and prostate contraction by ultrasonography Doppler that retrograde seminal fluid back flow to bladder with rhythmic prostate contraction, without anterograde ejaculation in second sample. First sample showed that there were none anterograde and retrogradeseminal flow and rhythmic prostate contraction. Third sample has rhythmic prostate contraction with reduced anterograde ejaculation.[21]

Alpha blocker used especially silodosin related with higher ejaculation disorder than other agents which not α1A receptor selective. One underlying mechanism are disruption closure at neck bladder when ejaculation period which caused retrograde ejaculate, and also insufficiency vas deferens contraction and seminal vesicle who predominantly innervated by α1A receptor.[19] Hisasue et al, demonstrated that α1A mRNA predominantly in human seminal vesicle between other subtype, so that decreasing seminal vesicle contraction capacity become one of another ejaculate disorder mechanism by alpha-1a blocker.[22]

This phenomenon in silodosin group was research by Homma et al. Patients who experience ejaculation disorder also have decrease IPSS score greater than others whose did not have that side effect, and there were no different drop out number.[23] Roehrborn et al, found that 28.1% patients who experience ejaculation disorders have significantly

not only improvement of LUTS complaint, but also better results of uroflowmetry examination compared with patients who did not have ejaculation disorders.[24]

Hisasue et al, investigated ejaculate after administration of silodosin and founded reduce ejaculate volume 80% and doesn't found retrograde seminal flow by ultrasonography Doppler. They suggest that ejaculatory disorders caused by adrenergic antagonists are caused by the turbulence of seminal fluid in the ejaculatory duct causing reduced emissions. This opinion was supported by ejaculate examination analysis result with lower fructose level, lower pH, reduce sperm concentration, and after all resulting emission problem.[22]

Limitation of this research were absent of urodynamic study, which can give more information than standard uroflowmetry. Besides that, almost all participants above 60 years old with moderate-severe LUTS, so the result could not be generalized for any younger patients or mild LUTS. Ultrasonography Doppler may necessary need in this study, to evaluate underlying cause of silodosin effect that impact to ejaculate disorders.

CONCLUSION

The administration of 8 mg of once daily silodosin has similar efficacy as 4 mg twice daily silodosin. There were no adverse events differences in the two groups. The most common side effect on giving of silodosin is ejaculation disorder.

REFERENCES

1. Wei J, Calhoun E, Jacobsen S. Urologic Diseases in America Project: Benign prostatic hyperplasia. J Urol. 2005; 173: 1256.
2. McVary K. BPH: Epidemiology and comorbidities. Am J Manag Care. 2006; suppl (12): S122.
3. Roehrborn CG, McConnell J. Etiology, pathophysiology, epidemiology and natural history of benign prostatic hyperplasia. In: Walsh P, Retik A, Vaughan E, Wein A,editors. Campbell's Urology. 10th ed. Philadelphia: Saunders; 2012. p. 2570–610.
4. Chute CG, Panser LA, Girman CJ, et al. The prevalence of prostatism: A population-based survey of urinary symptoms. J Urol. 1993;150:85–9.
5. Kok ET, Schouten BW, Bohnen AM, et al. Risk factors for lower urinary tract symptoms suggestive of benign prostatic hyperplasia in a community based population of healthy aging men: The Krimpen Study. J Urol. 2009;181:710–6.
6. Michel MC. The Pharmacological Profile of the α1A-Adrenoceptor Antagonist Silodosin. Eur Urol Suppl. European Association of Urology. 2010 Jul; 9(4): 486–90.
7. Chapple CR. BHP Disease Management. Introduction and concluding remarks. Eur Urol. 1999; 36(Suppl 3):1-6.
8. Brooks JD. 2002. Anatomy of the lower urinary tract and male genitalia: Campbell's Urology, 10th ed. Editor Walsh PC. Philadhelphia: WB Saunders Co; 2012. p. 41-80.
9. Pande S, Hazra A, Kundu AK. Evaluation of silodosin in comparison to tamsulosin in benign prostatic hyperplasia: A randomized controlled trial. Indian J Pharmacol. 2014; 46(6): 601–7.
10. Marks LS, Gittelman MC, Hill L a., et al. Silodosin in the Treatment of the Signs and Symptoms of Benign Prostatic Hyperplasia: A 9-Month, Open-label Extension Study. Urology. Elsevier Inc. 2009; 74(6): 1318–22.
11. Choo MS, Song M, Kim JH, et al. Safety and Efficacy of 8-mg Once-daily vs 4-mg Twice-daily Silodosin in Patients With Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Hyperplasia (SILVER Study): A 12-Week, Double-blind, Randomized, Parallel, Multicenter Study. Elsevier Inc. Urology. 2014;83(4):875-81.
12. Sato F, Furihata Y. Use of silodosin in a once daily administration for treating benign prostatic hyperplasia.Kissei Pharmaceuticals Co.,Ltd.2008; [007]:1-28.http://www.google.com/patents/WO2008106536A1?cl=en
13. European Medicines Agency. Silodyx (silodosin): EU summary of product characteristics. 2014. http://www.ema.europa.eu/.Accessed 8 Dec 2014.
14. Watson Pharma Inc. Rapaflo (silodosin) capsules: US prescribing information. 2013. http://www.actavis.com/. Accessed 8 Dec 2014.
15. Tatemichi S, Kobayashi K, Maezawa A, et al. a1-Adrenoceptor subtype selectivity and organ specificity of silodosin (KMD-3213) [in Japanese]. Yakugaku Zasshi. 2006;126:209–16.
16. Morganroth J, Lepor H, Hill LA, et al. Effects of the selective alpha 1a-adrenoreseptor antagonist silodosin on ECGs of Healthy men in a randomized, double-blind, placebo-and moxifloxacin-controlled study: A randomized controlled trial. Clin Pharmacol Ther. 2010, 87(5):609-13.
17. Chapple CR, Tubaro A, editors. Male LUTS/BPH Made Easy. London: Springer London; 2014.
18. Novara G, Tubaro A, Sanseverino R, et al. Systematic review and meta-analysis of randomized controlled trials evaluating silodosin in the treatment of non-neurogenic male lower urinary tract symptoms suggestive of benign prostatic enlargement. World J Urol. 2013; 31(4): 997–1008.
19. Chapple CR, Montorsi F, Tammela TLJ, et al. Silodosin therapy for lower urinary tract symptoms in

men with suspected benign prostatic hyperplasia: Results of an international, randomized, double-blind, placebo- and active-controlled clinical trial performed in Europe. Eur Urol. 2011; 59(3): 342–5.
20. Capogrosso I, Serino A, Ventimiglia E, et al. Effects of silodosin on sexual function-realistic picture from the everyday clinical practice. Andrology. 2015; 3: 1076–81.
21. Nagai A, Hara R, Yokoyama T, et al. Ejaculatory dysfunction caused by the new α1-blocker silodosin: A preliminary study to analyze human ejaculation using color Doppler ultrasonography. Int J Urol. 2008 Oct; 15(10): 915–8.
22. Hisasue SI, Furuya R, Itoh N, et al. Ejaculatory disorder caused by alpha-1 adrenoceptor antagonists is not retrograde ejaculation but a loss of seminal emission. Int J Urol. 2006; 13(10): 1311–6.
23. Homma Y, Kawabe K, Takeda M, et al. Ejaculation disorder is associated with increased efficacy of silodosin for benign prostatic hyperplasia. Urology. Elsevier Inc. 2010; 76(6): 1446–50.
24. Roehrborn CG, Kaplan S a, Lepor H, et al. Symptomatic and urodynamic responses in patients with reduced or no seminal emission during silodosin treatment for LUTS and BPH. Prostate Cancer Prostatic Dis. Nature Publishing Group. 2011; 14(2): 143–8.